ACUTE TOXICITY SUMMARY

CARBON MONOXIDE

(carbon monoxide)

CAS Registry Number: 630-08-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**23 mg/m³**
Critical effect(s)	angina in persons with known cardiovascular diseases who are exercising heavily
Hazard Index target(s)	Cardiovascular System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless gas
Molecular formula	CO
Molecular weight	28.01
Density	1.25 g/L @ 0°C
Boiling point	-191.5°C
Melting point	-205°C
Vapor pressure	>760 mm Hg @ 20°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in benzene, ethyl acetate, chloroform, acetic acid
Odor threshold	not applicable
Odor description	odorless
Metabolites	unknown
Conversion factor	1 ppm = 1.15 mg/m³ @ 25°C

III. Major Uses or Sources

Carbon monoxide (CO) is formed during the incomplete combustion of organic substances including gasoline, diesel, natural gas, wood, coal, tobacco, and other vegetation. The California Air Resources Board (CARB) Staff Report (1989) estimated that approximately 70% of the CO present in California urban atmospheres was due to emissions from mobile sources. Solid waste combustion, agricultural burning, and various industrial processes accounted for most of the remaining urban CO.

IV. Acute Toxicity to Humans

The severity of symptoms due to CO exposure increases with the blood carboxyhemoglobin (COHb) level. The first signs of CO exposure include mild headache and breathlessness with moderate exercise (HSDB, 1994). Continued exposure may lead to more severe headache, irritability, impaired judgment and memory, and rapid onset of fatigue (Winter and Miller, 1976). Persons with existing cardiovascular conditions, such as angina pectoris, are likely to be more sensitive to the effects of CO exposure. Earlier onset of angina was reported in exercising subjects with coronary heart disease exposed to 100 ppm (120 mg/m³) carbon monoxide (resulting in 2.9% blood COHb level) (Kleinman *et al*., 1989).

In another study, men with confirmed coronary artery disease and stable exertional angina were exposed to air with or without one of two levels of CO for 1 hour while at rest. They then exercised until the onset of angina (Allred *et al*., 1989). A 4.2% decrease in time to angina compared to control exercise periods ($p = 0.03$; 95% CI = 0.4-8.74) was observed following a 1-hour exposure to a mean concentration of 117 ppm (135 mg/m³) CO (resulting in 2% blood COHb level). Similarly, a 1-hour exposure to a mean concentration of 253 ppm (291 mg/m³) CO resulted in 4% blood COHb level and a 7.1% decrease in time to onset of angina compared to control exercise periods ($p = 0.002$; 95% CI = 5.18-14.46).

The California Ambient Air Quality Standard (CAAQS) for CO is based on the conclusion of the California Air Resources Board (CARB) (1982, 1989) that "exposure to carbon monoxide has been clearly demonstrated to cause aggravation of angina and other cardiovascular diseases. Carbon monoxide exerts its effect primarily by binding to hemoglobin and forming carboxyhemoglobin (COHb), thereby reducing the oxygen-carrying capacity of the blood. These effects are considered to be adverse and have been shown to occur at COHb levels in the range of 2.0 to 3.0 percent COHb." Aronow (1981) reported that the lowest demonstrated effect level for aggravation of angina was as low as 2% COHb.

In double blinded exposures (Benignus *et al*., 1987), 18 nonsmoking, young men at rest were exposed to high levels of CO in order to elevate COHb to levels of 15-20% in 3-5 minutes, followed by continued exposure to 232 ppm CO in order to maintain a constant COHb level for a total of 130 minutes, which resulted in COHb values of 16-23% (average = 19%). These values did not produce significantly more symptoms such as headache, dizziness, and nausea (as reported in open-ended questioning of the subjects) than in the control group ($n = 23$) exposed to air. The authors theorized that neurological symptoms reported for similar levels of COHb in the discussion of CO poisoning in medical standard references (cited in Benignus *et al*., 1987) may have resulted (1) from CO exposure in combination with exposure to other substance(s), (2) from stress, or (3) from higher COHb levels before the initial blood sample to measure COHb was taken.

Predisposing Conditions for Carbon Monoxide Toxicity

Medical: Persons with cardiovascular disease, including those with angina, persons with chronic obstructive pulmonary disease, persons with anemia, and fetuses may be more sensitive to the adverse effects of carbon monoxide exposure (CARB, 1982). The fetuses of pregnant women, especially those mothers exercising vigorously, may be especially vulnerable due to the much higher affinity of fetal hemoglobin for CO compared to adult hemoglobin.

Chemical: Persons exposed to methylene chloride are more sensitive to the effects of CO exposure because CO is a metabolite of methylene chloride. Smokers will experience an additional burden of COHb since their carboxyhemoglobin levels are already elevated by smoking.

V. Acute Toxicity to Laboratory Animals

Four-hour LC_{50}s for rats, mice, and guinea pigs are 1,807, 2,444, and 5,718 ppm (2,078, 2,811, and 6,576 mg/m^3) CO, respectively (Rose *et al*., 1970). The lowest reported lethal concentration in dogs (the level at which one dog in the group died) was 4,000 ppm (4,600 mg/m^3) CO for a 46-minute exposure (RTECS, 1994).

Anesthetized, open-chested dogs were exposed for 2 hours to air or to 100 ppm (120 mg/m^3) CO (Aronow *et al*., 1979). Postexposure blood COHb levels were 6.5%. Electrical shocks of varying amplitude were applied to the myocardium to induce ventricular fibrillation. A decrease in the ventricular fibrillation threshold was observed in CO-exposed dogs compared to controls.

A dose-dependent decrement in performance was observed in maze running in rats following a 30-minute exposure to 2,000, 3,000, 3,500, or 4,000 ppm (2,300, 3,500, 4,030, or 4,600 mg/m^3) CO (Annau, 1987). As exposure concentration increased, a greater proportion of rats failed to reach the goal and there was a decrease in goal directed behavior. The authors compare these results to lethargy and confusion observed in human victims following smoke inhalation.

VI. Reproductive or Developmental Toxicity

Carbon monoxide is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause developmental toxicity.

A prospective study of pregnancy outcomes reported an increased risk of fetal neurologic disorders following maternal CO poisoning. This resulted in blood COHb levels of 21% or greater with symptoms including, but not limited to, disorientation, depressed sensorium, limited and inappropriate response to simple commands, and coma (Koren *et al*., 1991).

Pregnant rats were exposed to 150 ppm (170 mg/m³) CO continuously for the duration of gestation (Fechter and Annau, 1980). The offspring of the CO exposed rats exhibited decreased birth weights and decreased growth rates prior to weaning. Behavioral testing revealed decreased performance on negative geotaxis (performing a 180° turn to face the top of an incline plane) and homing (orientation by the rat pup towards its home cage) tests in offspring of CO-exposed rats compared to controls.

Pregnant mice were exposed to 65, 125, 250, or 500 ppm (75, 144, 290, or 580 mg/m³) CO continuously on days 7-18 of gestation (Singh and Scott, 1984). A significant increase in fetal mortality was observed following maternal exposure to 500 ppm CO. A significant decrease in fetal body weight was observed following maternal exposure to CO at concentrations of 125 ppm or greater. Delayed ossification was observed in all dose groups but was not statistically significant or dose-dependent. No significant developmental effects were observed following maternal exposure to 65 ppm CO.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Level Protective Against mild adverse effects)

Because angina is a severe effect, there is no level protective against mild adverse effects.

Reference Exposure Level (level protective against severe adverse effects) :**20 ppm (23 mg/m³)**

Study	Aronow, 1981
Study population	humans
Exposure method	inhalation
Critical effects	aggravation of angina and other cardiovascular diseases
LOAEL	2% carboxyhemoglobin in blood
NOAEL	1.1%-1.3% carboxyhemoglobin in blood (corresponds to 20 ppm CO, calculated toxicokinetically)
Exposure duration	1 hour
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	20 ppm (23 mg/m³, 23,000 μg/m³)

Level Protective Against Life-threatening Effects

The NRC (1984) selected an EEGL of 400 ppm (460 mg/m³). The NRC document states that 400 ppm (460 mg/m³) was determined as the concentration of CO to which a 1-hour exposure would result in a carboxyhemoglobin (COHb) level of less than 10% in resting individuals. The committee cautions that sensitive individuals, such as persons with angina or heart disease, should not be exposed to concentrations approaching the EEGL as they may incur serious adverse health effects. The Coburn model (Coburn *et al*., 1965) estimates that only at a low ventilation rate (e.g., 5 liters/ min) would a 1-hour exposure to 400 ppm CO result in a COHb of less than 10%. At a ventilation rate of 15 liters/min, the same exposure would be expected to result in 16% COHb (Shusterman, 1994). The NRC (1984) acknowledged that at the EEGL of 400 ppm physical activity might increase the COHb to 20% or higher by 1 hour. The exposure level of 400 ppm may not protect sensitive subpopulations, since persons with cardiovascular disease would experience serious health effects such as angina pectoris (Aronow, 1981; Allred *et al*., 1989). According to NRC (1984), "It must also be stressed that, in people with atherosclerosis, the danger of myocardial infarction, angina pectoris, or even sudden death might be increased by exposure to CO." The EEGL of 400 ppm is recommended as the level protective against life-threatening effects with a cautionary note that people with heart disease, as noted by NRC, may not be protected. In addition, the NRC notes that the EEGL is derived for resting individuals. Individuals engaged in activities other than resting will achieve a higher COHb level and will beat increased risk.

VIII. References

Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, *et al*. Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Health Effects Institute (HEI) Research Report No 25. Cambridge (MA): HEI, 1989.

Annau Z. Complex maze performance during carbon monoxide exposure in rats. Neurotoxicol Teratol 1987;9:151-155.

Aronow WS, Stemmer EA, Zweig S. Carbon monoxide and ventricular fibrillation threshold in normal dogs. Arch Environ Health 1979;34(3)184-186.

Aronow WS. Aggravation of angina pectoris by two percent carboxyhemoglobin. Am Heart J 1981;101:154-157.

Benignus VA, Kafer ER, Muller KE, Case MW. Absence of symptoms with carboxyhemoglobin levels of 16-23%. Neurotoxicol Teratol 1987;9(5):345-348

(CARB) California Air Resources Board. California Ambient Air Quality Standards for carbon monoxide (sea level). Sacramento: CARB; 1982.

(CARB) California Air Resources Board. Adequacy of the statewide carbon monoxide ambient air quality standard: The impact of recent health effects studies. Staff report. Sacramento: CARB; December 1989.

Coburn RF, Forster RE, Kane PB. Considerations of the physiology and variables that determine the blood carboxyhemoglobin concentration in man. J Clin Invest 1965;44(11):1899-1910.

Fechter LD, Annau Z. Prenatal carbon monoxide exposure alters behavioral development. Neurobehavioral Toxicol 1980;2:7-11.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 7/31/94).

Kleinman MT, Davidson DM, Vandagriff RB, Caiozzo VJ, Whittenberger JL. Effects of short-term exposure to carbon monoxide in subjects with coronary artery disease. Arch Environ Health 1989;44(6):361-369.

Koren G, Sharav T, Pastuszak A, Garrettson LK, Hill K, Samson I, *et al*. A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. Reprod Toxicol 1991;5:397-403.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

(NRC) National Research Council. Committee on Toxicology. Emergency and continuous exposure limits for selected airborne contaminants. Vol 4. Washington (DC): National Academy Press; 1984.

(RTECS®) Registry of the Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health, Cincinnati (OH) (CD-ROM Version). Denver (CO): Micromedex, Inc; 1994. (Edition expires 7/31/94).

Rose CS, Jones RA, Jenkins LJ, Siegel J. The acute hyperbaric toxicity of carbon monoxide. Toxicol Appl Pharmacol 1970;17:752-760.

Shusterman D. Personal communication. Aug 6, 1994.

Singh J, Scott LH. Threshold for carbon monoxide induced fetotoxicity. Teratology 1984;30:253-257.

Stewart RL. The effect of carbon monoxide on humans. Annu Rev Pharmacol 1975;15:409-423.

Winter PM, Miller JN. Carbon monoxide poisoning. JAMA 1976;236(13):1502-1504.